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Case of Ovarian Hyperstimulation Syndrome complicated by a Heterotopic Quadruplet Pregnancy

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ABSTRACT

Summary: Ovarian hyperstimulation syndrome (OHSS) is a serious complication of ovulation induction associated with significant morbidity and requires prompt recognition and treatment. We present an unusual case of OHSS complicated by a heterotopic quadruplet pregnancy including a cervical pregnancy.

Case Description: 30-year-old female, Gravida 1 Living children 0 Miscarriage 1 with a history of anovulation and secondary infertility. Her prior infertility work-up showed a normal hysterosalpingogram with patent fallopian tubes, a normal semen analysis, anovulation with polycystic ovaries on ultrasound. After the maximum dosage of letrozole failed to induce ovulation, she conceived with combined letrozole and low-dose gonadotropins without complications, but unfortunately the pregnancy ended in a spontaneous miscarriage. Three years later, after again failing ovulation induction with maximum-dose letrozole she consented to treatment with a combination of letrozole and low-dose gonadotropins for three days. Ultrasound showed 2 mature and 2 smaller follicles prior to human chorionic gonadotropin (hCG) trigger and insemination. Ten days later, the patient presented to an outside emergency department with nausea, abdominal pain, decreased urine output, negative urine pregnancy test and was diagnosed with urinary tract infection. At 4 weeks gestation, she had additional symptoms of shortness of breath, tachycardia, abdominal distention, 10-pound weight gain and a positive urine pregnancy test. Imaging revealed bilaterally enlarged ovaries and ascites with a hematocrit of 62% and urine specific gravity 1.032. Severe OHSS was diagnosed and she was started on heparin and aspirin. Multiple paracentesis removed 6 L of ascitic fluid. At 5w1d, two gestational sacs were identified. After vaginal bleeding at 7w6d, ultrasound showed two intrauterine, one non-viable cervical pregnancy and a left sided adnexal mass consistent with ectopic pregnancy. Laparoscopic left salpingectomy and ectopic removal was performed. The cervical pregnancy passed, and a second miscarriage of one of the uterine pregnancies occurred at 14 weeks. Ultimately, she had a healthy, preterm vaginal delivery at 36w3d. This case highlights a rare presentation of OHSS complicated by a multifetal heterotopic pregnancy.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a rare, serious complication of controlled ovulation induction in assisted reproductive technology. OHSS has historically been associated with in vitro fertilization (IVF), estimated to occur in approximately 1-5% of IVF cycles. After the introduction of antagonist protocols for ovulation suppression combined with luprolide acetate trigger and freeze-all cycles, the incidence of OHSS in IVF patients declined. It is rarely seen with ovulation induction (OI) using oral medications with low-dose gonadotropins and intrauterine insemination (IUI). OHSS is characterized by the stimulation of multiple follicles which lead to increased ovarian size as well as stimulation of an inflammatory response, release of vascular endothelial growth factor and activation of the renin-angiotensin-aldosterone system. These vascular permeability changes result in the severe presentation of the syndrome. OHSS is staged by the severity of symptoms and ranges from mild, moderate to severe. Mild OHSS can cause abdominal distention with abdominal pain, nausea, and vomiting due to increased ovarian size; however, it often resolves within 7-10 days or with the following menstrual cycle. Moderate-to-severe OHSS is characterized by massive fluid shifts from the intravascular to extravascular spaces. This can result in hypovolemia, electrolyte imbalances, hypercoagulability and development of edema, ascites, pleural and pericardial effusions. OHSS can be further subdivided into early- and late-onset. Early-onset typically occurs within 4-7 days of the hCG ovulatory trigger and resolves with the next menses. Late-onset OHSS often begins at least 9 days after the hCG trigger in the setting of a pregnancy and is exacerbated by the rising hCG, which can lead to a more serious presentation as in our case presented here [1-6].

CASE PRESENTATION

This 30-year-old female Gravida 0 initially presented to clinic for evaluation of infertility for 1 year. Her evaluation revealed a normal hysterosalpingogram with bilateral tubal patency, a normal semen analysis, and anovulation. Her history of anovulation, coupled with hirsutism and an ultrasound confirmed polycystic ovaries (PCOS) with an antral follicle count (AFC) bilaterally. Past medical history was notable for obesity (BMI 39) and vitamin D deficiency. She underwent OI at a maximum letrozole dose of 7.5 mg; however, no ovulation occurred based on the absence of follicular growth on ultrasound and a mid-luteal progesterone of 0.3 ng/mL. IVF with an antagonist protocol using a luprolide trigger and a planned freeze-all cycle was strongly recommended. Due to financial limitations, the patient opted for letrozole with low-dose gonadotropin IUI. IUI was then performed and resulted in a pregnancy that ended in an early pregnancy loss.

The patient then stopped fertility treatment for 3 years prior to returning to clinic for reevaluation. In the interim, the patient underwent gastric sleeve surgery, subsequently lost 60 pounds, and represented with a BMI of 29. Patient was still amenorrheic at this time. Repeat hysterosalpingogram was normal and the ultrasound confirmed polycystic ovaries with AFC >30. She again failed ovulation induction with maximum dosages of oral medication. IVF with an antagonist protocol and a luprolide trigger with a freeze-all cycle was again recommended. The patient and partner elected for OI with letrozole 5 mg cycle day 3-7 and purified follicle stimulating hormone (FSH) 50 IU on cycle day 5, 7, and 9 followed by low-dose HCG 5,000 IU trigger. She had serial ultrasounds and serum estradiol levels to monitor for follicular development. Ultrasound showed 2 mature follicles, measuring 15 and 17 mm, and 2 smaller

follicles on cycle day 10. A low-dose hCG 5,000 IU trigger shot was given on cycle day 12, and IUI was performed on cycle day 14.

Ten days later, the patient presented to an outside emergency department with nausea, abdominal pain, and decreased urine output with a negative urine pregnancy test. She was diagnosed with a urinary tract infection, treated with antibiotics and discharged home. Two days later, she represented to the outside hospital with additional symptoms of shortness of breath, tachycardia, abdominal distention, a 10-pound weight gain and a serum hCG of 147. Abdominal ultrasound revealed bilaterally enlarged ovaries, ascites, and bilateral pleural effusions (Figure 1). Initial labs revealed hemoconcentration, hypoalbuminemia, and elevated AST as noted in Table 1.

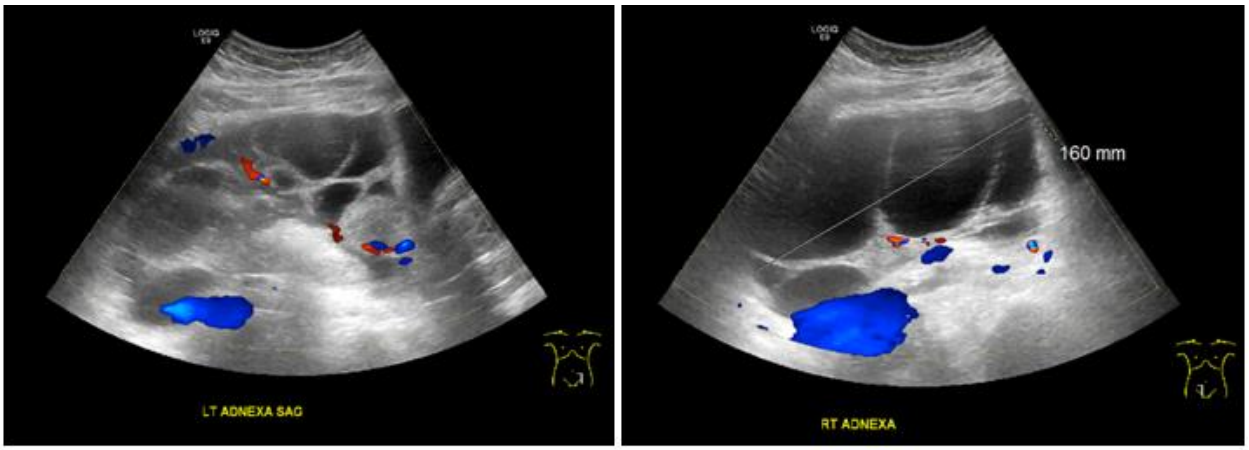

Figure 1: Abdominal ultrasound on Hospital Day #4. Abdominal ultrasound revealed bilaterally enlarged ovaries, ascites, and bilateral pleural effusions. Left image is the left ovary (170 x 90 cm). Right image is the right ovary (160 x 100 cm).

Table 1: Initial Lab Values of OHSS Patient at Outside Emergency Room (Estimated Gestational Age = 3 weeks 5 days).

Labs	Value	Reference Range
White Blood Cells	24.8	4.8 - 11.0 /nL
Hemoglobin	20.8	12.0 - 16.0 g/dL
Hematocrit	62	36.0 - 46.0 %
Serum creatinine	1.54	0.52 - 1.04 mg/dL
Glomerular Filtration Rate (GFR)	40	>=60 mL/min/1.73m²
Sodium	133	137 - 145 mmol/L
Potassium	5.3	3.5 - 5.3 mmol/L
Aspartate Aminotransferase (AST)	64	14 - 36 units/L
Alanine aminotransferase (ALT)	17	<=34 units/L
Albumin	3.3	3.5 - 4.8 g/dL
Urine specific gravity	1.02	1.003 - 1.035
Urine pregnancy test	Negative	Negative

* EGA= Estimated gestational age. GFR= glomerular filtration rate.

She was diagnosed with early pregnancy complicated by severe OHSS, was started on anticoagulation with Lovenox 60 mg, aspirin 81mg daily, and IV albumin then was transferred to our hospital. Abdominal ultrasound revealed

bilaterally enlarged ovaries and abundant ascites (Figure 1). She had two paracentesis procedures with a total of 4 liter of straw-colored fluid removed. The course of her laboratory values and treatment during the acute phase of her hospitalization from 3 weeks 5 days gestation to 4 weeks 3 days gestation are summarized in Table 2. Three days later when the pregnancy was at 4 weeks 3 days gestation, she had recurrence of symptoms with abdominal swelling and discomfort. She was started on IV albumin rotating with IV mannitol every 6 hours then had an additional two liters of ascites removed via paracentesis. She was discharged with overall improvement, minimal ascites noted on ultrasound, good urine output, stable vital signs, and normalized laboratory tests. She was started on vaginal progesterone suppositories nightly.

Table 2: Labs Results during Severe Ovarian Hyperstimulation Syndrome Admission from 3 weeks 5 days to 4 weeks 3 days gestation.

EGA	Hct (36.0-46.0%)	Urine SG (1.003-1.035)	Albumin (3.5-4.8 g/dL)	hCG (mIU/mL)	Treatment
3w5d	62	1.02	3.3	Negative UPT	Treated for urinary tract infection
4w0d	53.9	1.038	3.2	147	IV albumin 25 g with 500 mL normal saline, Aspirin 81 mg, Lovenox 80 mg. Paracentesis with 4.0 L removed.
4w1d	45	1.025	2.1	164	Lovenox 60 mg IV daily, Aspirin 81 mg daily, albumin 25 g IV with normal saline
4w2d	38.7	1.02	2.5		Continue IV albumin, Lovenox, Aspirin
4w3d	33.2	1.01	2.8	239	Paracentesis 2.0 L removed. Discharged following morning.

EGA = Estimated gestational Age; hCG= human chorionic gonadotropin; Hct = hematocrit; SG = specific gravity. IV = intravenous.

At her clinic follow-up at 5weeks 1 day gestation, the ultrasound identified two gestational sacs. At 7 weeks 0 days, the patient presented with vaginal bleeding and 3 gestational sacs were noted with one sac in the cervix and two gestational sacs in the uterus (Figure 2). At 7 weeks 6 days follow-up and ultrasound confirmed twin intrauterine pregnancy, the previously noted cervical pregnancy, with a left sided adnexal mass measuring 2.9 x 2.4 cm concerning for an ectopic pregnancy. She was consented for and underwent a minimally invasive procedure with left salpingectomy with removal of an intact ectopic pregnancy. During this admission, fetus #1 was noted to be in the cervical canal with no fetal cardiac activity. Fetus #1 passed without complication during this admission, and fetus #2 and #3 remained in the endometrial cavity. At 14 weeks, patient had a spontaneous miscarriage of fetus #2. Ultimately, the patient had an uncomplicated vaginal delivery of a healthy, preterm infant at 36 weeks 3 days.

DISCUSSION

OHSS is a rare but potentially life-threatening condition in its most severe form. Early recognition and prompt treatment are crucial for prevention of serious complications. Baseline risk factors include a history of polycystic ovaries, previous ovarian hyperstimulation, antral follicle count >24 and antimullerian hormone >3.4. During IVF additional risk factors include >17 follicles over 10 mm at the trigger, elevated estradiol >3500 pg/ml at trigger and

>15 oocytes retrieved[6]. In the setting of pregnancy, patients are more likely to develop late-OHSS and the disease course can be prolonged due to the continued hCG exposure. However, most cases will resolve within the first trimester with close observation. Based on the higher levels of hCG in multifetal gestations, there is an increased incidence of late-onset OHSS. Reviewing this case, our patient had risk factors for OHSS including polycystic ovaries, elevated antral follicle counts, increased AMH level, and multifetal gestation. The incidence of severe OHSS in the setting of OI and IUI is rare with only a few cases reported in the current literature [4,5]. Currently, no cases exist describing a heterotopic multifetal pregnancy complicated by OHSS in the setting of OI.

This case highlights the risks of OI in patients with PCOS, even when using oral medications and low-dose gonadotropins. Although methods to prevent severe OHSS in patients undergoing IVF have advanced, including antagonist protocols with luprolide acetate triggers and freeze-all cycles, these procedures do not apply in patients undergoing IUI. Our patient previously underwent OI with letrozole and gonadotropins 50IU for three non-consecutive days and conceived. Although she miscarried, she did not have any symptoms of OHSS but suffered an early miscarriage. She had ultrasound documentation of two mature and two immature follicles on ultrasound before low-dose hCG trigger but still released four oocytes that were fertilized after IUI. We continue to counsel our patients at high risk for OHSS about safer IVF protocols using antagonist protocols with luprolide triggers and freeze-all cycle, but these treatments are time-consuming and expensive, thus not available to all patients. Some centers advocate the use of in-office aspiration of any follicles greater that two prior to trigger and IUI7, however this has not been popularized. More commonly dopamine agonists are used for the prevention of OHSS in patients at risk for OHSS8. This case of OHSS complicated by a heterotopic, multifetal pregnancy included a cervical pregnancy that was spontaneously lost, an ectopic pregnancy that was successfully removed, and an early second trimester loss, ultimately provided our patient with a near-term healthy liveborn.

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